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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/521,805 | 01/21/2005 | Katja Wosikowski-Buters | 2923-686 | 3802 |

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ROTHWELL, FIGG, ERNST & MANBECK, P.C.
1425 K STREET, N.W.
SUITE 800
WASHINGTON, DC 20005

| EXAMINER | |
|---|---|
| KISHORE, GOLLAMUDI S | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1615 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 12/18/2007 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

PTO-PAT-Email@rfem.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/521,805 | WOSIKOWSKI-BUTERS ET AL. | |
| | Examiner | Art Unit | |
| | Gollamudi S. Kishore, Ph.D | 1615 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *28-49 and 53-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-49 and 53-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 10.26.07
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The amendment dated 10-26-07 is acknowledged.

Claims included in the prosecution are 28-49 and 53-56.

In view of the amendments to the claims, the rejections involving Henkin and the 112 rejection are withdrawn.

### *Claim Rejections - 35 USC § 103*

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 28-37, 41-48 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723).

WO 00 teaches the claimed compounds (Examples in English equivalent). WO further suggests that these compounds can be incorporated into the membranes of liposomes and facilitate the targeting of cytotoxic agents such as doxorubicin (0069 of English equivalent). What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids. Since the amounts of the active agent depend upon the condition of the patient and the nature of the disease, it would have been obvious to one of ordinary skill in the art to vary the amounts in order to obtain the best possible results. The use of phospholipids as the liposome forming

material would have been obvious to one ordinary skill in the art since phospholipids are routinely used for the formation of liposomes.

Applicant's arguments and the declaration submitted have been fully considered, but are not persuasive. Applicant argues the following:

> "U.S. Published Application 2003/0013723 is directed to 3-amidino phenylalanine derivatives as urokinase inhibitors. It is disclosed at paragraph 0069 of U.S. 2003/0013723 that it is possible to incorporate the 3-amidino phenylalanine derivatives into the membrane of carrier vesicles, i.e., liposomes, to facilitate targeting of active substances enclosed in carrier vesicles. Paragraph 0069 is the only part of U.S. 2003/0013723 that discloses a vesicle or liposome.
>
> Present claim 28 of the instant application requires a liposomal formulation of 3-amidino-or 3-guanidino phenylalanine derivatives. Furthermore, present claim 28 now recites the limitation that the phenylalanine derivatives of general formula I are encapsulated within the liposome. Applicants submit that liposomal encapsulation of the phenylalanine derivatives is distinct from the disclosure of U.S. 2003/0013723, wherein it is possible to incorporate, or embed, the phenylalanine derivatives into the membrane of a carrier vesicle or liposome.
>
> U.S. 2003/0013723 is silent with respect to the encapsulation of the phenylalanine derivatives of general formula I within a liposome. One of skill in the art would recognize from U.S. 2003/0013723 that the phenylalanine derivatives, when embedded in a membrane of a liposome, would serve as a target for lymphocytes. One of skill in the art would also recognize that the present claims require the phenylalanine
>
> derivatives to be an active pharmaceutical ingredient that is encapsulated within a liposome, which is different and distinct from the disclosure of U.S. 2003/0013723.
>
> To further support Applicant's position, Applicants hereby submit an opinion declaration of Wolfgang Schmalix (a co-inventor of the present application) for the Examiner's consideration. This declaration essentially states that one of skill in the art would recognize the therapeutic difference between phenylalanine derivatives embedded in the membranes of liposomes (as described in U.S. 2003/0013723) and phenylalanine derivatives encapsulated by liposomes (as required by the present claims)".

These arguments are not persuasive. It is well-known in the art that the lipophilic active agents are encapsulated within the bilayer membrane of the liposomes and the hydrophilic agents in the aqueous interior. The term, 'encapsulated' is used for both lipophilic active agents within the membrane and the active agents in the aqueous compartment. The examiner cites the references of Leigh, 6,599,527 (col. 3, lines 10-

13), Janjic, 6,168,778 (col. 17, line 49 through line 8; Weiner, 5,049,392 (col. 2, lines 48-56); Yau-Young, 5,023,087 (col. 9, lines 45-58) in this context. Furthermore, it would appear that most of the claimed compounds are lipophilic and thus, one would expect their sequestration within the membrane bilayer. Instant specification has only one example and it is unclear from the example where the tested compound is located within the liposome. Furthermore, the prior art recognizes the compounds to be anti-neoplastic agents (0001) and therefore, whether they are used for targeting or not would still have the ability as anti-neoplastic agents.

Applicant's arguments that the administration of the liposomal formulation required by present claim 28 surprisingly leads to prevention of undesirable side effects such as hemolysis and US 2003 is silent with respect to the side effects are not persuasive. That liposomes reduce the hemolysis of active agents is well -known in the art. The examiner cites the references of Ben-Hur, 6,010,890 (col. 6, lines 63-65); Kurono, 4,906,477 (col. 4, lines 10-13) in this context. Therefore, what is observed by applicant is to be expected and not an unexpected finding.

3. Claims 28-32 and 41-48 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723) in combination with WO 88/09168.

WO 00 as pointed out above teaches the claimed compounds (Examples in English equivalent). WO further suggests that these compounds can be incorporated into the membranes of liposomes and facilitate the targeting of cytotoxic agents such as

doxorubicin (0069 of English equivalent). What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids. Since the amounts of the active agent depend upon the condition of the patient and the nature of the disease, it would have been obvious to one of ordinary skill in the art to vary the amounts in order to obtain the best possible results. The use of phospholipids as the liposome forming material would have been obvious to one ordinary skill in the art since phospholipids are routinely used for the formation of liposomes.

WO 88 teaches liposomal formulations containing doxorubicin for the treatment of tumors. The liposomes contain lecithin, phosphatidylglycerol, cholesterol and cryoprotectant. WO teaches that the liposomes can be dehydrated and reconstituted before use (Examples 1 and 2).

One of ordinary skill in the art would be motivated to use the liposomes of WO 82 containing lecithin, phosphatidylglycerol, cholesterol and a cryoprotectant in the generic teachings of WO 00 with a reasonable expectation of success since WO 82 teaches that the liposomes made from those components can be used for tumor treatment purposes.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding US 2003. Applicant argues that the combination with Huang would lead to a liposome that comprised 3-amidino phenylalanine derivatives embedded in the liposome membrane to

facilitate targeting of the active substances enclosed in the liposome as taught in 2003. This argument has already addressed by the examiner. Furthermore, Huang is combined for its teachings of the liposomal composition which the primary reference doesn't specifically teach and for its teachings of cryoprotectant and applicant has not shown that the instant liposomal composition is different from the prior art composition.

4. Claims 28-49 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 00 04954 (English equivalent US 2003/0013723) in combination with Barenholz (6,156,337).

WO 00 as pointed out above teaches the claimed compounds (Examples in English equivalent). WO further suggests that these compounds can be incorporated into the membranes of liposomes and facilitate the
targeting of cytotoxic agents such as doxorubicin (0069 of English equivalent). What is lacking in WO is the teaching of the amounts the active compound in the liposomes and whether the liposomes are unilamellar with claimed diameters. WO is also silent with respect to the specific components forming the liposomes, that is, phospholipids.

Barenholz teaches liposomal formulations containing DMPG, phosphatidylcholine and cholesterol for the delivery of active substances and the advantages of using these phospholipids. The liposomal formulations contain a cryoprotectant and are dehydrated (col. 7, lines 15-28; col. 9, lines 19-57).

It would have been obvious to use the phospholipids taught by Barenholz in the generic liposomes taught by WO 00 because of the advantages taught by Barenholz.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding US 2003. Applicant argues that the combination with Barenholz would lead to a liposome that comprised 3-amidino phenylalanine derivatives embedded in the liposome membrane to facilitate targeting of the active substances enclosed in the liposome as taught in 2003. This argument has already addressed by the examiner. Furthermore, Barenholz is combined for its teachings of the liposomal composition which the primary reference doesn't specifically teach and for its teachings of cryoprotectant and applicant has not shown that the instant liposomal composition is different from the prior art composition.

**5. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is

(571) 272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Woodward Michael can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/ G Shore

Gollamudi S Kishore, Ph.D
Primary Examiner
Art Unit 1615

GSK